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PRACTICAL AND THEORETICAL IMPLICATIONS BASED ON
LONG-TERM FOLLOW-UP OF MÉNIÈRE'S PATIENTS
TREATED WITH STREPTOMYCIN SULFATE*

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SUMMARY

THE PROBLEM

Four patients who had received streptomycin sulfate in the treatment of Ménière's disease were evaluated in terms of the long-range effects of therapy and utilized as experimental subjects.

FINDINGS

None had experienced a return of symptoms over the entire follow-up period which ranged from 11 to 13 years. There was residual tinnitus, and deafness ascribable to the disease and ataxia ascribable to toxic effects of the drug as well as the disease.

In the three subjects who had one normal ear each, there was no effect of the streptomycin on the hearing in that ear but considerable suppression of semicircular canal function with some recovery.

In all of the five diseased ears there was a slight significant improvement in hearing (later lost in one) but great suppression of semicircular canal function with little recovery.

Otolith function, as measured by ocular counterrolling, was within the normal range in two subjects and greatly suppressed in two. Although tests were not carried out prior to therapy, it was believed that the suppression was due more to disease than the drug.

When exposed to bizarre stimulation of the semicircular canals in the SRR none were susceptible to canal (motion) sickness, but the three with unilateral disease perceived the Coriolis illusion. The findings utilizing a new ataxia test battery were similar to those obtained in persons with complete loss of vestibular function. Inasmuch as the greatly differing degree of otolith function bore no relation to these test results, they were ascribed mainly to loss of canal function.

An attempt was made to interpret the findings in terms of the etiology of idiopathic Ménière's disease, and the suggestion was put forth that it might represent a disturbance attributable to the secretory cells of the crista.

ACKNOWLEDGMENTS

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INTRODUCTION

Eight patients who had been given streptomycin sulfate parenterally in the treatment of Ménière's disease by Schuknecht were re-examined and the findings reported in 1957 (1). These patients had been followed for periods varying between fourteen and fifty-two months after the drug was administered to the point of suppression of semicircular canal function with resulting ataxia. The noteworthy findings reported in 1957 (hereafter termed the first follow-up) were freedom from vertiginous attacks in all eight patients, significant improvement in auditory thresholds in four of the five with unilateral disease and in one of the three with bilateral. There was no loss of hearing in either the normal or diseased ears.

Four of these eight patients agreed to come to the Naval Aerospace Medical Institute in 1963 (second follow-up) for medical evaluation and to participate in experiments. Approximately two years later, a limited opportunity was taken (third follow-up) to inquire into the status of these subjects in connection with an experiment carried out in Cambridge, Massachusetts.

The present report deals with the follow-up studies of these four patients. The purpose was twofold: first to gather information on the effects of streptomycin sulfate in the treatment of Ménière's disease and, second, to identify those experimental subjects who have presumed preservation of otolith function but whose semicircular canal function is suppressed.

PROCEDURE

The functional status of the semicircular canals was determined during the second follow-up by means of the threshold caloric test (2) which was scored as the temperature of the thermal stimulus nearest to body temperature that caused a definite nystagmic response. The functional status of the otolith organs was measured by ocular counter-rolling (3), and bodily equilibrium was assessed by utilizing a new ataxia test battery (4). Susceptibility to canal (motion) sickness was estimated in the Slow Rotation Room by means of the dial test (5,6). In the same Room were recorded the subjects' perceptions of two variants of the oculogyral illusion (7,8), one termed the Coriolis illusion, which have their genesis in the semicircular canals. During the experiment at Cambridge, threshold caloric and ataxia tests were given to three of the four patients.

Details regarding the method of administering the various tests, their scoring, and their significance are given in the next section of this report.

RESULTS

SCHUKNECHT'S FINDINGS

These are summarized in Table I; additional details concerning the audiometric and caloric tests will be presented under these headings. The symptomatology was severe in all cases and was typical of idiopathic Ménière's disease except in patient KI. His attacks had some of the features of migraine, namely, visual disturbance and headache which were followed by drowsiness.

Schuknecht administered streptomycin sulfate to the point of complete suppression of response to the caloric test in the diseased ear in those with only one ear affected, which also resulted in a greatly diminished response in the normal ear; in KI, with bilateral disease, there was complete suppression on the left and greatly reduced response on the right. Spontaneous nystagmus was noted with the beat directed away from the ear with the greater decrease in caloric response. Early symptoms precipitated by treatment were loss of appetite and nausea, in that order. None experienced an increase in tinnitus, a known precursor of loss of hearing, but all experienced an increase in ataxia which was the only permanent side effect of streptomycin therapy.

GENERAL STATUS DURING FOLLOW-UP PERIODS

In the interval between the first and second follow-up none of the patients had a recurrence of any symptoms characteristic of Ménière's disease (Table II). There was, however, persistence of slight deafness, ataxia, and tinnitus although none categorized these symptoms under "complaints." Two manifested mild cardiovascular abnormalities which, in all probability, were unrelated to Ménière's disease. At the time of the "third follow-up" all were in good health, and it was possible to carry out ataxia and threshold caloric tests on three.

TEST RESULTS

Hearing

The audiometric findings are summarized in Figures 1-4. The three subjects with unilateral disease did not manifest any significant changes in the normal ear although in CA there was a decrease in the auditory threshold of more than 10 db at low frequencies. Patient OC, who had registered a significant decrease in auditory threshold in the diseased ear at the time of the first follow-up, reverted to the pretreatment level while the other two, who had manifested insignificant changes on the first follow-up, registered striking decreases in threshold on the second. The subject with bilateral disease not only held the improvement in hearing indicated at the first follow-up but experienced a slight further improvement on the right.

Table 1

SCHUKNECHT'S FINDINGS IN FOUR PATIENTS WITH MÉNIÈRE'S DISEASE														
Subject	Age	Duration of symptoms	Discrimination (%)	Recruitment	Caloric responses before treatment		Streptomycin		Ataxia	Return to full work load (mos.)	Caloric response after treatment		Recurrence	Follow up (mos)
					Diseased	Normal	Total grams	Days			Diseased	Normal		
Unilateral														
OC	38	10 mo.	36	C*	Decr.	Norm.	22½	7½	++	2	Lost	Gr.decr.	No.	48
CA	39	12 yr.	34	C	Decr.	Norm.	54	26	++	4	Lost	Gr.decr.	No.	31
AN	48	1 yr. 6 mo.	70	C	Decr.	Norm.	28	14	+++	9**	Lost	Gr.decr.	No.	25
Bilateral														
KI	32	5 yr. - R. 5 yr. - L	74R 84L	—	Decr.	Decr.	45	24	+++	2½	Gr. decr.	Gr.decr.	No.	35

* C = Complete

** Psychoneurosis contributed to prolonged morbidity.

Table II

MEDICAL FINDINGS AT TIME OF SECOND FOLLOW-UP STUDY																		
SUBJECT	SEX	PRESENT AGE	FOLLOW-UP (YEARS SINCE THERAPY)	INTERVAL HISTORY			MOTION SICK SUSCEPTIBILITY		OTOSCOPIC EXAM.	WEBER	RINNE	RETINOSCOPIC EXAM.	SIZE	HEART			Hgb gm %	URINALYSIS
				VERTIGINOUS ATTACKS	FITNESS FOR HARD WORK*	SYMPTOMS	PRE-THERAPY	POST-THERAPY						Blood Pressure	MURMUR	ECG VCG		
OC M	50	11 1/4		NONE	MOD.	Sl.tin. Sl.atx.	<<av.	NIL	NO ABN	L.	ac>bc	INC. LIGHT REFLEX	N	160 / 100	NONE	LVH ischemia	14.5	neg.
CA F	49	9 3/4		NONE	GOOD	Sl.tin. Sl.atx.	<av.	NIL	NO ABN	MID	ac>bc	NO ABN	N	125 / 80	sys.ejc. M&A I-II	NO ABN	11.5	neg.
AN M	56	9 1/3		NONE	GOOD	Sl.tin. Sl.atx.	<<av.	NIL	NO ABN	MID	ac>bc	NO ABN	N	138 / 78	NONE	NO ABN	16	neg.
KI M	42	9 3/4		NONE	GOOD	Sl.tin. Sl.atx.	NIL	NIL	NO ABN	MID	ac>bc	tort.A& V. INC. LIGHT REFLEX	N	150 / 110	NONE	Sl. LVH	15	neg.

★ Subject's estimate

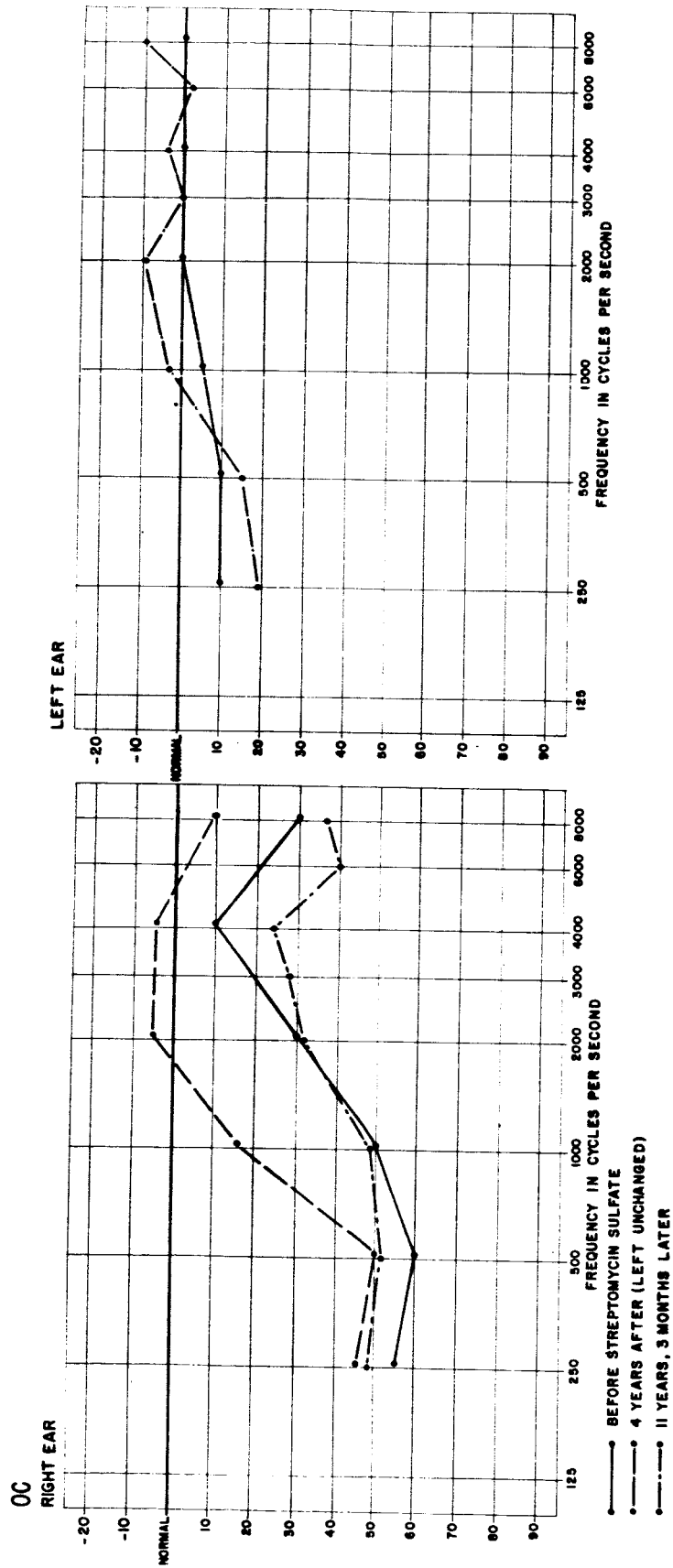


Figure 1

Audiograms of Patient OC before and after Administration of Streptomycin Sulfate

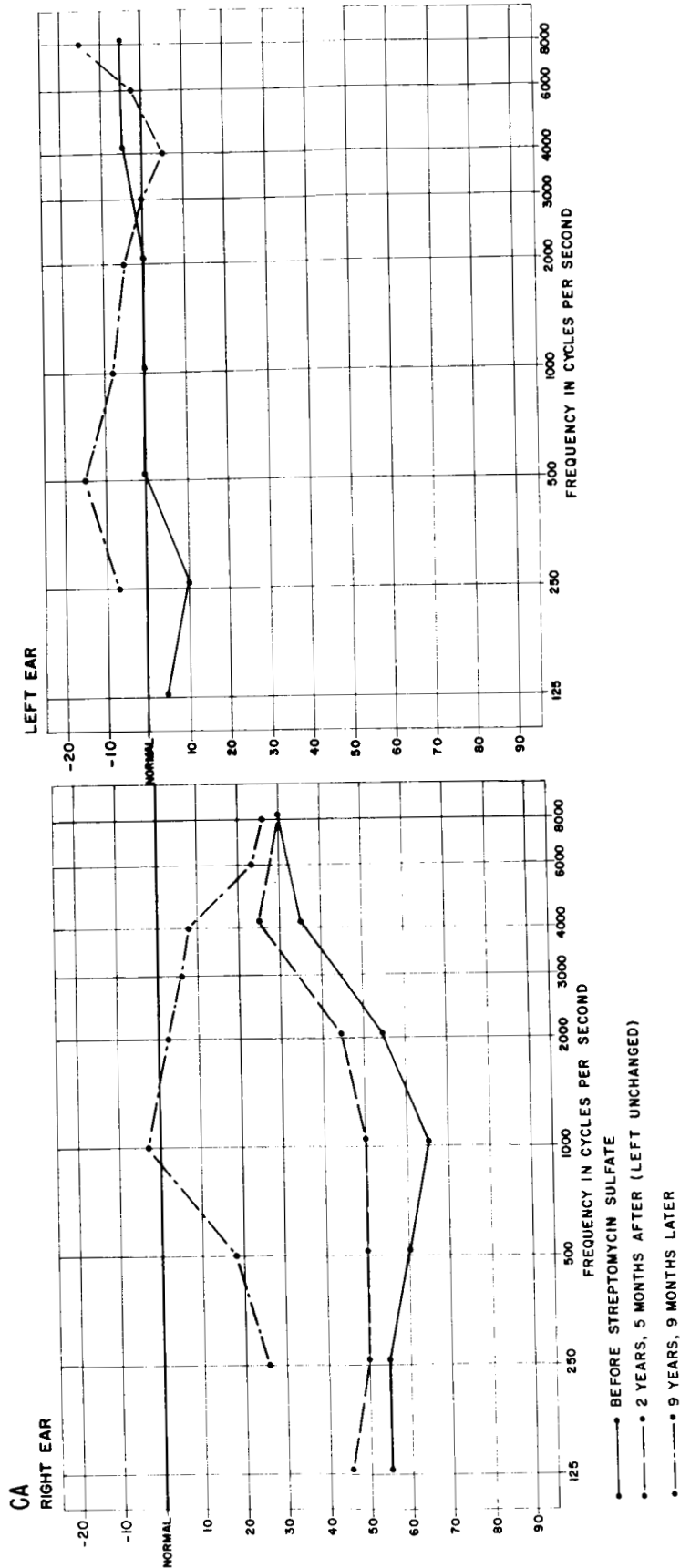


Figure 2

Audiograms of Patient CA before and after Administration of Streptomycin Sulfate

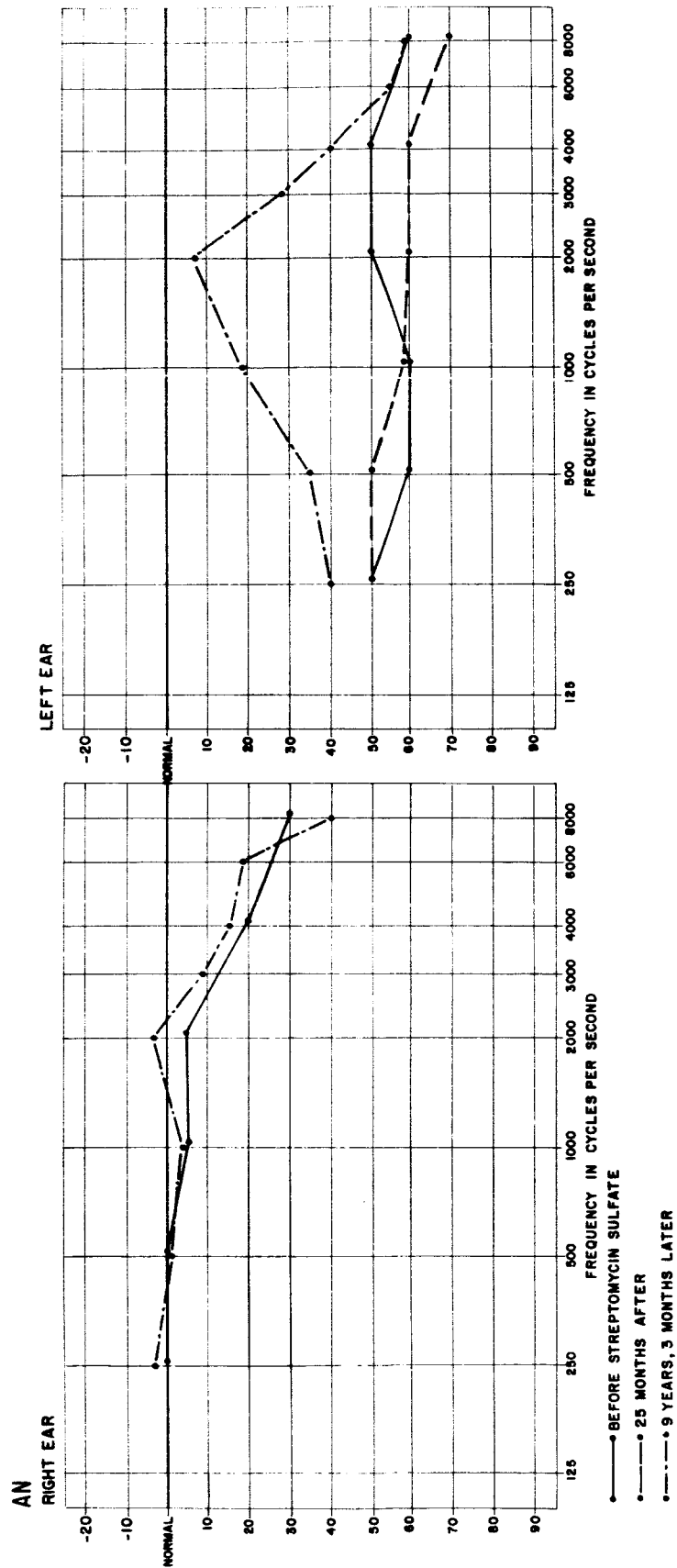


Figure 3

Audiograms of Patient AN before and after Administration of Streptomycin Sulfate

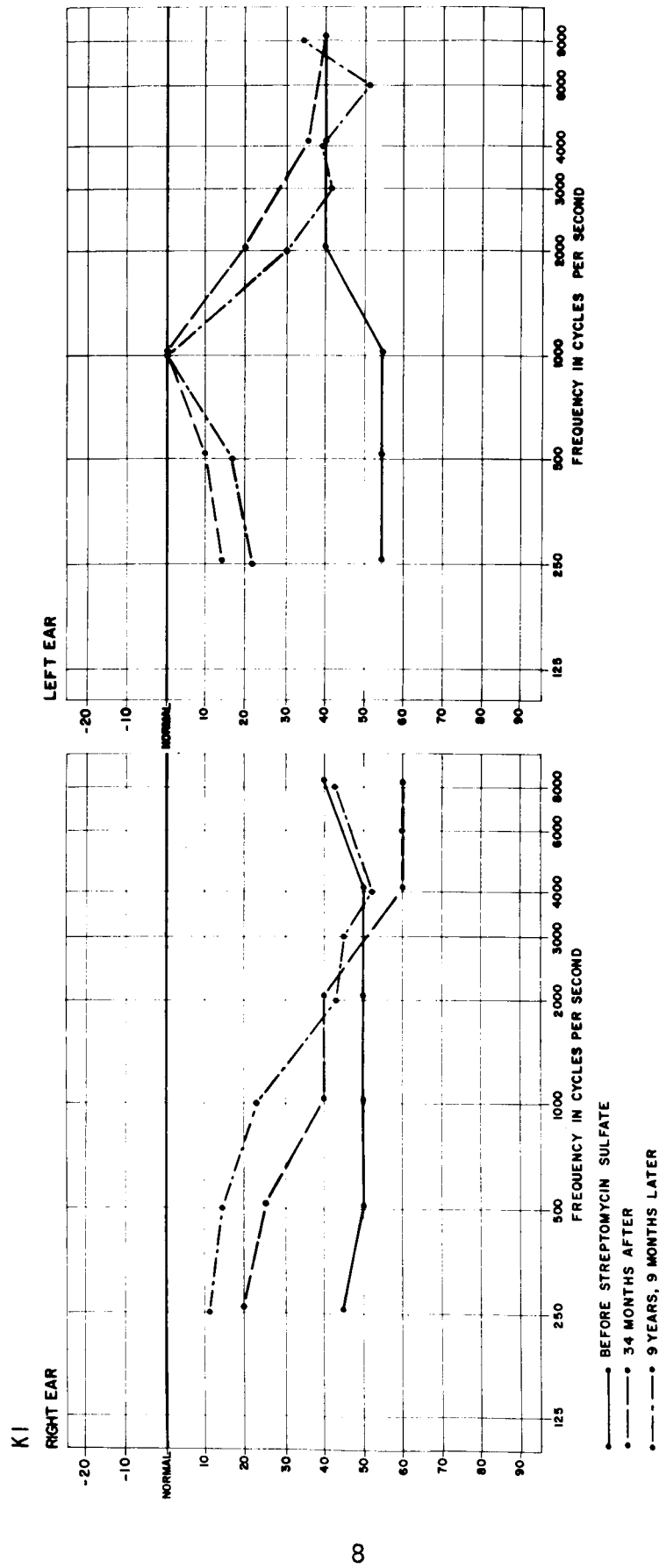


Figure 4

Audiograms of Patient KI before and after Administration of Streptomycin Sulfate

Comment. The absence of any measurable hearing loss in the normal ears indicates that streptomycin sulfate did not destroy any significant number of cochlear hair cells or indeed any related structural element essential to their function. This lack of toxicity was strongly emphasized by the fact that there was improvement in hearing on the diseased side. Thus, even the combined effect of disease, "injury," and drug "toxicity" was insufficient to result in loss of function; indeed, the effect of the drug was salutary. The time-course of the changes in auditory threshold in the diseased ears is of particular interest. In three instances there was a significant decrease and in one an increase in threshold between the first and second follow-up, a period ranging from two to four years. Important implications are 1) the injurious agent, although "active," must have been of an exceptionally mild character; 2) these effects, direct or indirect, must have taken place with almost incredible slowness; 3) the most likely location was in the peripheral organ where the basic integrity of many sensory receptors was maintained although function depressed; and 4) prolonged follow-up in these cases is essential to determine the evolutionary changes.

Semicircular Canals

The functional status of the semicircular canals based on the caloric test is shown in Table III. In the early tests, including the first follow-up, the procedure consisted essentially of measuring the duration of nystagmus following irrigation with water at 80° F or "ice water" contained in a syringe which had been cooled by contact with crushed ice. In subsequent "threshold" tests, the response to cold water was measured in terms of the highest irrigating temperature at which nystagmus was evoked. The temperature was measured at the exit nozzle. At the time of the second follow-up the lowest temperature used was 12° C, and at the third follow-up, 8° C.

Administration of the drug resulted in suppression of response which was greater in the diseased than normal ears with the exception of complete suppression on the normal side in OC. At the time of the first follow-up there was evidence of recovery of function in the normal ears which was striking in OC and only slight in the others. There was "good recovery" of function in only one of the five diseased ears. In the second and third follow-up examinations the only unexpected finding was the decrease in function on the normal side in OC. It was concluded that the cause of the decrease, occurring some time in the four to eleven years after therapy, was far more likely to be due to some incident other than Ménière's disease or to a delayed response to the drug.

Comment. Comparative data on squirrel monkeys are of interest. In one experiment (9) eight animals were given streptomycin sulfate to the point where there was no nystagmus response to ice water in ten ears, and the threshold response in the remaining six ears ranged from 19° C to 24° C. Over a period of six months or more there was recovery of response to the threshold levels prior to administration of the drug in all but four ears, and in these the threshold levels had risen to 30° - 32° C. Pathological studies revealed loss of hair cells in the sensory epithelium of the cristae in all animals, varying from very slight to severe.

Table III

CALORIC TEST RESULTS BEFORE AND AFTER STREPTOMYCIN SULFATE														
Subject	EAR	Before Therapy		Time Max. Effect of Drug		First Follow — up			Second Follow — up			Third Follow — up ⁴		
		Temp.	Nys(sec)	Temp.	Nys(sec)	Mos. after Therapy	Temp. °C	Nys. (sec)	Yrs. after Therapy	Temp. °C	Nys. (sec)	Yrs. after Therapy	Temp. °C	Nys. (sec)
OC	R(d)	80°F	30"	ICE WATER	NIL	48	1-W	83"	11 ¹ / ₄	30.6	th ¹	13 +	31.3	th
	L(n)	80°	120"	1-W	NIL		1-W	110"		12.0	NIL		8.5 ⁵	th
CA	R(d)	80° ²	60"	1-W	NIL	34	1-W	NIL	9 ³ / ₄	12	NIL			
	L(n)	80° ²	85"	1-W	80"		1-W	90"		25	th			
AN	R(n)	80° 1-W	80" 110"	1-W	65"	25	1-W	75"	9 ¹ / ₃	31.5	th	11 ¹ / ₄	32.6	th
	L(d)	80° 1-W	NIL 40"	1-W	NIL		1-W	NIL		12	NIL		8.2 ⁵	> th
KI	R(d)	80°	90"	1-W	40"	35	1-W	2"	9 ³ / ₄	12 ³	NIL	12	16.5	th
	L(d)	80°	65"	1-W	NIL		1-W	60"		12 ³	NIL		17.0	th

1 = threshold response; typical normal temp. = 35 — 36.5 °C

2 = 3rd day of streptomycin treatment

3 = severe pain despite codeine; irrigation shortened

4 = limited to caloric and ataxia tests

5 = irrigation for 3 minutes

It would seem that, in man, recovery of a normal threshold response is less likely than in the squirrel monkey, although more data on man are needed. In both animals and man it would appear that the very slow phase of the lowering of the threshold response must be the result of central compensation.

Otolith Organs

Under rigidly controlled test conditions it has been demonstrated not only that ocular counterrolling is a specific or nearly specific indicator of otolith function but also that test-retest reliability is good (10). The results may be expressed: 1) in absolute values, 2) as a counterrolling index (C-1) defined as one-half the maximum right and left ocular torsion, and 3) right-left asymmetry. The range of counterrolling index values for 100 normal subjects (11) at a tilt of 25° and 50° has been found to be 183-626, with a mean of 344 minutes of arc, and for ten subjects with bilateral vestibular defects (10), 21 to 126 with a mean of 68. Threefold right-left differences were sometimes observed. With rare exception, the roll at 50° tilt was greater than that at 25° , and in these exceptional cases the magnitude of the roll at 25° was notably great.

The results of this test, obtained at the time of the second follow-up, are plotted in Figure 5 where the shaded area indicates the normal range. Only CA (Index 127) shows abnormal right-left asymmetry; on leftward tilt the counterroll at 25° is greatly suppressed and at 50° , nil. The findings in OC (Index 305) were "normal," although they could represent a reduction in counterroll compared with that prior to his illness. The counterrolling values for AN (Index 235) fall within the normal range, but they are far below the mean. Counterrolling is clearly reduced below normal in KI, although there is good left-right asymmetry.

Comment. Inasmuch as counterrolling measurements were not obtained prior to streptomycin therapy, one can only speculate as to the relative etiological significance of the disease process and drug therapy in causing the reduction in otolith function. Based on a very small experience, we can state that the counterrolling index is significantly below normal in subjects manifesting loss of hearing and suppression of canal function confined to one side. This suggests that in OC, and probably AN, there is bilateral function of the maculae and that any reduction in function is far more likely to have been due to the disease injury rather than drug toxicity. The large reduction in counterrolling can be explained for KI on the basis of bilateral disease. The great reduction in CA might be explained either on the basis of complete destruction of the maculae on the diseased side due to disease or unusual susceptibility to the toxic effect of streptomycin combined with disease injury.

In the squirrel monkey experiment referred to above (9) only three of the eight animals that received large doses of streptomycin showed pathological changes in the maculae. In each instance it was very slight; the macula of the saccule was affected in three and in one of these the utricle also was affected. The same predilection for the

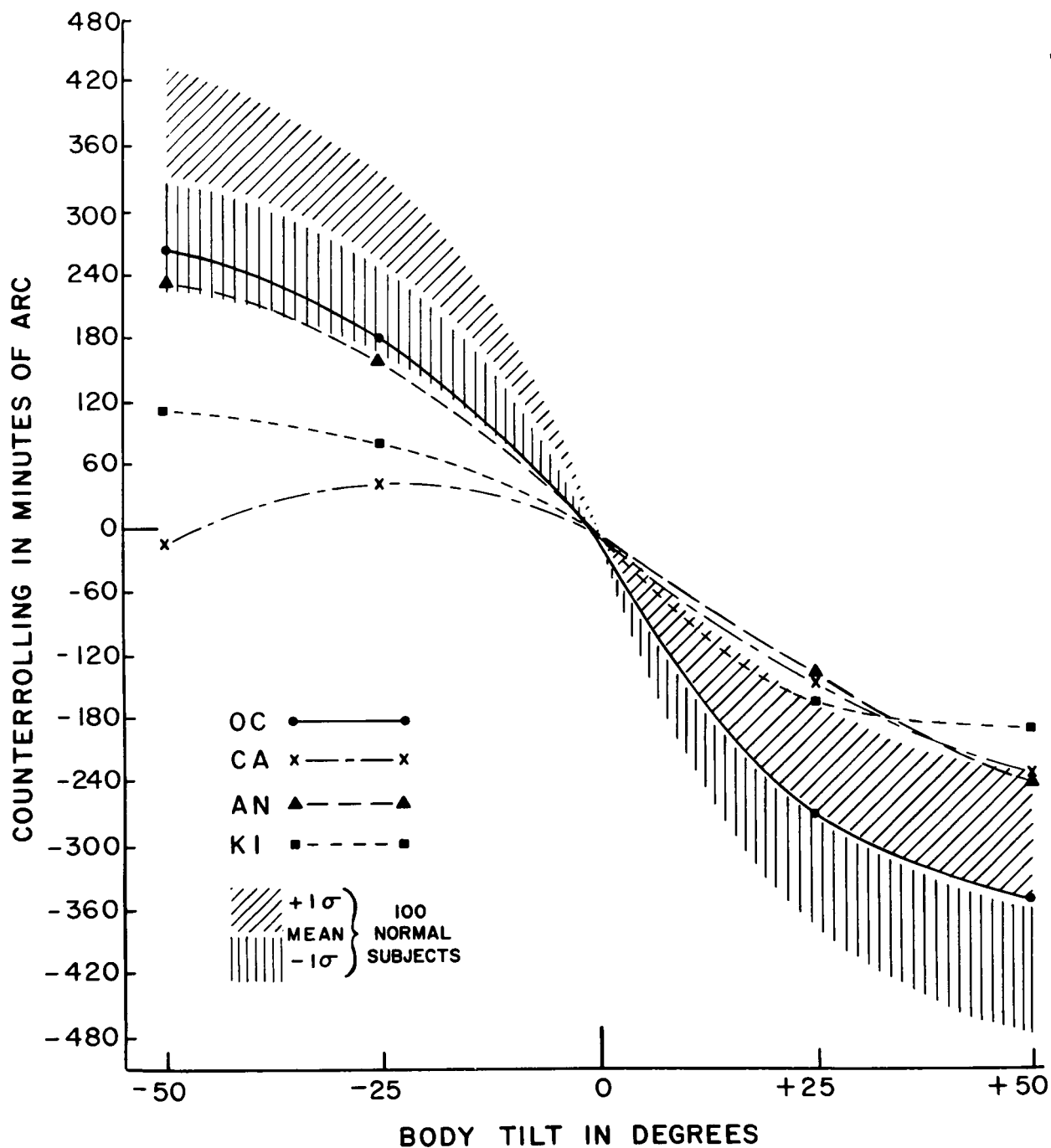


Figure 5

Ocular Counterrolling Response to Body Tilt Measured in Patients OC, CA, AN, and KI During Second Follow-Up Study (Mean Values) and in 100 Normal Subjects (Mean Values ± 1 S. D.)

semicircular canals has been demonstrated when streptomycin was administered to cats (12, 13) but not in guinea pigs (14) where the receptors in the cristae and utricle were equally affected. Insofar as the results on animals might be extrapolated to man, it would tend to minimize the etiological role of streptomycin in causing a suppression of otolith end organ function.

Ataxia Test

The subjects performed all tests (4) in the following sequence: 1) Classical Romberg Test, consisting of standing with eyes closed, arms at sides, and feet together on the floor for a period of sixty seconds; 2) Sharpened Romberg Test (SR), consisting of standing on the floor with eyes closed for sixty seconds in the stringent body position of body erect or nearly erect, arms folded against chest, feet in heel-to-toe position and tandemly aligned; 3) Test Battery (Short Version), also performed in the stringent body position, consisting of walking with eyes open (Walk H/T Test) on a $\frac{3}{4}$ " wide rail, standing with eyes open (Stand E/O Test) on the $\frac{3}{4}$ " wide rail, and standing with eyes closed (Stand E/C Test) on a $2\frac{1}{4}$ " wide rail; 4) standing on one leg for thirty seconds with eyes closed and arms folded against chest (SOLEC). The best three out of five trials constituted the scoring of the Test Battery (Short Version), and weighted scores were used for the SR and SOLEC tests. Maximum scores available were as follows: Classical Romberg: 60 seconds; SR: 240 (60 x 4) seconds; Walk H/T: 15 (steps); Stand E/O and Stand E/C tests: 180 (seconds); SOLEC: 150 seconds (30 seconds x 5 trials). The tests were repeated on several daily occasions to determine the extent of improved performance with practice.

Results from all four patients tested during the second follow-up and three of the four, tested in 1965, are summarized in Tables IV and V.

Classical Romberg Test: All four subjects obtained perfect scores; i.e., they stood on the floor for a period of sixty seconds with eyes closed.

Walk H/T Test: Three of the subjects scored within the average normal range, but only one of these three (AN) improved appreciably with practice (133%). The fourth subject, KI, initially scored at the 2nd percentile, but he improved so considerably with practice (225%) that his improved score fell within the high average range (82nd percentile).

Stand E/O Test: None of the subjects' initial scores fell within the average range. All four subjects improved sufficiently with practice to produce scores within the average range, although such improvements were not always maintained. Subject KI, who scored poorest initially among the subjects, showed improvement with practice at a level consistent with the improvement levels shown by the other three subjects.

Table IV

SERIAL ATAXIA TEST SCORES IN FOUR STREPTOMYCIN TREATED
PATIENTS AT TIME OF SECOND AND THIRD FOLLOW-UP

SUBJECT	FOLLOW-UP PERIOD	TEST SESSIONS	WALK HEEL/TOE		STAND EYES OPEN		STAND EYES CLOSED		SHARPENED ROMBERG		SOLEC** RIGHT		SOLEC LEFT	
			Score	Percentile	Score	Percentile	Score	Percentile	Score	Percentile	Score	Percentile	Score	Percentile
OC	II	1	12	70th	7	5th	8	1st	11	1st	—	—	11	1st
	II	2	5	7th	12	30th	10	1st	12	1st	—	—	—	—
	II	3	9	40th	10	20th	11	1st	26	1st	—	—	9	1st
	III	1	6	17th	6	4th	8	1st	18	1st	10	1st	12	1st
	III	2	5	13th	9	17th	8	1st	12	1st	13	4th	19	17th
	III	3	8	35th	9	17th	6	1st	15	1st	15	8th	12	1st
	III	4	11	74th	9	17th	9	1st	21	1st	13	4th	14	4th
	III	5	13	87th	10	35th	7	1st	17	1st	12	4th	16	8th
	Max. Improvement		8 per cent	71 per cent			38 per cent	136 per cent			50 per cent		73 per cent	
	II	1	13	90th	8	10th	11	10th	6	9th	12	3rd	—	—
CA	II	2	8	30th	13	35th	12	15th	16	19th	11	1st	—	—
	II	3	8	30th	9	15th	8	2nd	7	9th	12	3rd	—	—
	Max. Improvement		0 per cent	63 per cent			9 per cent	167 per cent			0 per cent		—	—
AN	II	1	3	18th	6	7th	6	1st	9	1st	13	4th	—	—
	II	2	4	20th	9	30th	7	1st	14	1st	—	—	—	—
	II	3	4	20th	6	7th	5	1st	8	1st	14	6th	—	—
	III	1	6	17th	13	65th	7	1st	9	1st	12	4th	11	1st
	III	2	7	26th	9	17th	6	1st	10	1st	12	4th	8	1st
	III	3	6	17th	13	65th	8	1st	9	1st	17	8th	21	17th
	Max. Improvement		133 per cent	117 per cent			33 per cent	56 per cent			31 per cent		91 per cent	
	II	1	4	2nd	8	1st	10	1st	12	1st	11	1st	—	—
	II	2	6	5th	6	1st	12	1st	17	1st	13	1st	—	—
K1	II	3	7	7th	14	13th	9	1st	10	1st	13	1st	—	—
	III	1	4	2nd	7	5th	7	1st	12	1st	14	4th	14	2nd
	III	2	7	22nd	9	12th	9	1st	12	1st	13	3rd	13	1st
	III	3	10	48th	14	43rd	7	1st	13	1st	13	3rd	12	1st
	III	4	13	82nd	12	31st	7	1st	15	1st	12	3rd	12	1st
	III	5	13	82nd	13	36th	13	10th	9	1st	11	1st	16	3rd
	Max. Improvement		225 per cent	75 per cent			30 per cent	42 per cent			27 per cent		14 per cent	

II Indicates Second Follow-up, 1963

* This Subject's Period II Percentiles are based on a succeeding normative age group to which he advanced since Period I.

III Indicates Third Follow-up, 1965

** SOLEC—Stand one leg eyes closed

Table V

MEAN POSTURAL EQUILIBRIUM (ATAXIA) TEST PERFORMANCE DIFFERENCES BETWEEN A GROUP OF MÉNIÈRE'S TREATED INDIVIDUALS AND A GROUP OF AGE-MATCHED, RANDOMLY SAMPLED NORMALS					
TEST	NORMALS	MÉNIÈRE'S	MEAN DIFF.	U	P
WALK H/T	10.5	8.0	2.5	7	—
STAND E/O	24.8	7.3	17.5	0	.02
STAND E/C	65.8	8.8	57.0	0	.02
SR	143.5	9.5	134.0	0	.02
SOLEC	64.5	11.8	52.7	0	.02

Stand E/C Test: Initially, three of the subjects scored at the 1st percentile, and despite 30 to 38 per cent improvement with practice, their scores remained at the 1st percentile. The fourth subject, CA, initially scored at the 10th percentile, and although a gain of 9 per cent improvement was shown, the improvement was not maintained.

Sharpened Romberg Test: Consistent with findings on the Stand E/C Test, initially the same three subjects scored at the 1st percentile, and despite the very marked improvements ranging from 42 to 136 per cent their scores remained at the 1st percentile level. Subject CA initially scored at the 9th percentile, and while an improvement of 167 per cent was realized, this improvement was not maintained.

SOLEC Test: All four subjects initially scored at between the 1st and 4th percentile. One subject (CA) failed to improve with practice; the three remaining subjects improved 14 to 91 per cent with practice, but nevertheless the corresponding percentile levels either did not change (subject KI) or improved only very slightly (subjects AN and OC).

Although the subjects all made poor scores, there were intragroup differences. The over-all rank order was CA best, KI worst, with the others falling between. With reference to the residual vestibular functions, it would appear that there was no correlation as far as otolith function is concerned. Although there was a clear difference between KI with severe bilateral suppressed function of the canals and the remaining three subjects with greater residual function on one side, other factors may have accounted for the difference. In all likelihood, there was nothing to choose between caloric threshold levels (one ear) of 25° to 31.5° C, all representing severe depression in terms of ataxia.

Comment. These four individuals as a group, in comparison with a group of age-matched individuals randomly sampled from a normal population, performed poorer on all of the postural equilibrium (ataxia) tests (Table V), and on all of the tests except Walk H/T the mean performance differences were statistically significant ($P < .02$ by U test). The performance of KI was similar to that of subjects with bilateral suppression of both canal and otolith function (15) and that of the remaining three was only slightly better.

Habituation as Indicated by the Oculogyral Illusion

This illusion has been defined (7) as an apparent movement of objects in the visual field resulting from stimulation of the semicircular canals by angular acceleration and has been shown to be related to involuntary eye movements (16). One characteristic type of this illusion is perceived when a person, rotating about one axis, tilts his head about a second axis. This simultaneous rotation of the head about two axes constitutes an effective but bizarre stimulus to the semicircular canals, involving not only the oculogyral illusion but also symptoms characteristic of motion sickness as well.

This illusion has been used as an indicator in previous experiments carried out in the Slow Rotation Room (SRR). This room rotates counterclockwise and if a subject, fixating a luminous target in the dark while rotating at constant velocity, tilts his head toward the left shoulder, the target will appear to rise. It was learned early on that subjects habituated to this illusion (17), and experiments were devised to study the nature and characteristics of this adaptation. The investigation was conducted in the rotating room and required that an otherwise immobile subject tilt his head in a systematic manner over a period of hours until the illusion was greatly reduced or extinguished. When this was done it was found that, after cessation of rotation, the same head movement would still evoke an illusion but in the opposite direction; tilting the head to the right evoked no response (Figure 6). These findings indicated that habituation involved a compensatory response, and the fact that it was elicited after cessation of rotation indicated it was also a conditioned response. Inasmuch as nausea and other side effects restricted the number of head movements in a given period of time using normal subjects, the opportunity was taken to repeat the experiment using the Ménière's subjects who were insusceptible to the nausea syndrome.

The object was to determine if habituation would occur in a matter of minutes. The subjects, seated in the dark, fixated, at a distance of about 8 feet, a 6-inch cube illuminated within and dimly outlined by a series of small holes along the edges as perceived in the dark; with cube slightly canted, the "height" was $5\frac{1}{2}$ inches. Estimates of apparent movement were made in terms of units equal to the height of the box. Estimates were made before, during rotation at 10 RPM, and after cessation of rotation moving the head toward the shoulder. The practice movements during rotation were experimenter-paced at the rate of $12\frac{1}{2}$ full movements every minute. They were continued until the illusion was extinguished or negligible in amount.

The results for three subjects are summarized in Table VI; KI did not perceive the illusion. The results are clear in showing habituation to the illusion within periods ranging from about three to twenty-five minutes and involving 38 to 250 head movements. The number of movements is in line with the results of previous experiments (17) although individual variance is too great to draw further comparisons. There was some indication that habituation extended beyond the first experimental day as shown by decreasing illusory effects on successive days. It would appear that the findings in AN demonstrated that habituation was in the nature of a compensatory and conditioned response. It was not clearly evident for the other two subjects. This is not out of line with previous findings (17) which demonstrate individual variance.

Comment. One additional observation deserves mention. Prior to carrying out the experiment just described the subjects were exposed to angular accelerations in the plane of the horizontal pair of canals by causing the SRR to accelerate to 10 RPM in about eight seconds, and, after a period of at least two minutes at constant velocity, to decelerate in about five seconds. Not only were the illusory responses greatly reduced in comparison with the normal, but two of the three did not regularly perceive the oculo-gyral illusion in the horizontal plane. It came as a surprise therefore that they perceived

Table VI

ALTERATION IN PERCEPTION OF THE OCULOGYRAL ILLUSION AS THE RESULT OF TILTING HEAD TO LEFT SHOULDER ABOUT ONCE EVERY 5 SECONDS WHILE ROTATING COUNTER CLOCKWISE AT 10 RPM IN THE SLOW ROTATING ROOM											
SUBJECT	EXPERIMENTAL DAY	SRR STATIONARY		10 RPM					Shortly after Cessation of Rotation		
				Shortly after Start		Prior to Stop					
		HEAD LEFT	HEAD RIGHT	HEAD LEFT	HEAD RIGHT	NUMBER HEAD MOVEMENTS COMPLETED	RESPONSE HEAD LEFT	HEAD LEFT	HEAD RIGHT	HEAD LEFT	HEAD RIGHT
OC	1	Sl. Rot.	Sl. Rot.	2 [★] 1	1/2 1	125 (10min.)	NIL	1/2 1	1/2 1	NIL	NIL
	2	NIL	NIL	1 1	1/2 1	70 (4'50")	NIL	NIL	NIL	NIL	NIL
	3	Sl. Rot.	Sl. Rot.	2/3 1	2/3 1	38 (3'5")	NIL	NIL	NIL	NIL	NIL
CA	1	Sl. Rot.	Mod. Rot.	2 1	1 1	172 (13'50")	NIL	1/2 1	1/2 1	1/3 1	1
	2	Sl. Rot.	Sl. Rot.	1 1/2 1	2 1	106 (8'30")	Sl. 1	NIL	NIL	NIL	NIL
AN	1	NIL	NIL	3 1	2 1	250 (25min) [★]	Sl. 1	2 1	2 1	1/2 to 1/2 right	1
	2	NIL	NIL	1/2 1	1/2 1	104 (8'15")	NIL	1/2 1	1/2 1	1/2 1	1
	3	NIL to 1/2 1	NIL	1 1	1/2 1	150 (12 min)	NIL	1 1	1 1	NIL	NIL

★ Distance in terms of width (5 1/2") of target

★ Error in pacing

COMPARATIVE MAGNITUDE AND DIRECTION OF THE CORIOLIS ILLUSION ASSOCIATED WITH SINGLE HEAD MOVEMENTS BEFORE, DURING AND AFTER PROLONGED ROTATION AT 5.4 RPM. TESTS CARRIED OUT AT 7.5 RPM.

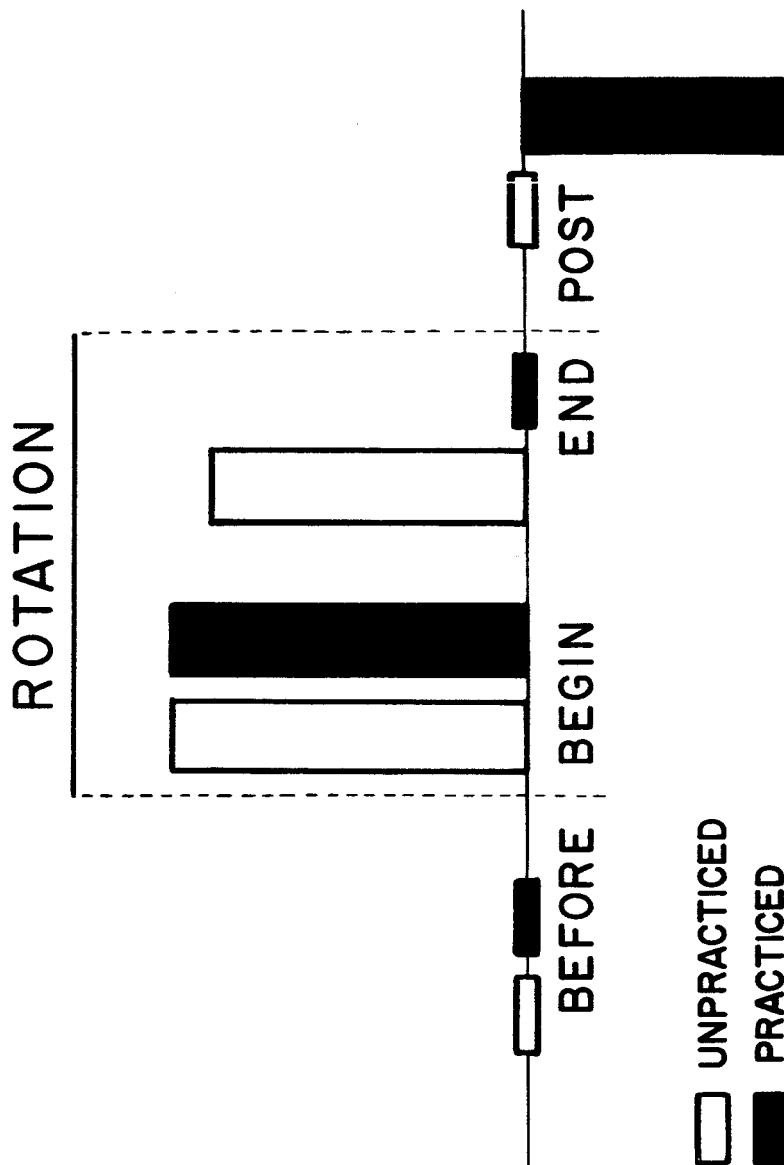


Figure 6

the oculogyral illusion as readily as normal subjects when the head was rotated simultaneously about two axes. There are two possible explanations for the difference: first, that the horizontal canal may have been more severely damaged than the vertical canals, and second, that only one (horizontal) canal was involved when the angular accelerations were in that plane but that more than one canal was involved in the Coriolis type of acceleration. The possibility of differentially testing the canals by this method is suggested.

Susceptibility to Motion Sickness

Even prior to streptomycin therapy the subjects had not experienced much motion sickness although none had been exposed to very stressful force environments. Following therapy, there not only was no history of motion sickness but also none experienced the nausea syndrome in the SRR while carrying out the dial test (5,6) or as a result of habituation to the oculogyral illusion. The dial test involved an experimenter-paced task in which the subject was required to set five different dials so placed around a seat that it involved maximum rotations of the head out of the plane of the room's rotation. One hundred such settings while the subjects were rotating at 10 RPM did not produce any characteristic symptoms of motion sickness which persons with normal vestibular organs would, in all likelihood, have experienced. This insusceptibility to canal (motion) sickness was in line with previous findings, indicating that even slight suppression of canal function prevented the nausea syndrome.

DISCUSSION

The effects of streptomycin therapy in these patients must have significance in terms of the etiology of "idiopathic" Ménière's disease. The salient emergent facts were abolition of acute attacks associated with suppression of semicircular canal function and followed by lowering of the auditory threshold in all of the diseased ears. Information concerning the "attacks" was based mainly on the subjective symptomatology, hence, furnished only a gross indicator of disease injury and drug toxicity; the caloric and audiometric test findings, however, provided information often below the level of subjective awareness. The former indicated severe depression of canal function in all diseased ears shortly after administration of the drug with little or no recovery save in one instance. Changes in audiometric threshold, however, occurred over a period of several years and, in one instance, initial "improvement" was lost. Although tests of otolith function were not carried out until many years after therapy, there was indirect evidence that the drug caused little or no macular suppression save possibly in one subject.

Theoretically, the therapeutic activity of streptomycin might have been due to its antibiotic effect on microorganisms or by virtue of its toxic effects on structural elements of the auricular sensory systems. In the absence of any information implicating a microorganism in idiopathic Ménière's disease, even a "cure" resulting from the exhibition of an antibiotic is insufficient proof of an infectious agent although it imposes a requirement to rule it out.

Regarding the second possibility, there was evidence of toxic destruction involving the canalicular system in the diseased ears. By extrapolating from relevant investigations on animals, we can say that the sensory epithelium over the cristae, especially the hair cells themselves, are most vulnerable. Indeed, this predilection raises the possibility that "drug ablation" prevented symptoms simply by reducing the sensory input. While this might account for vertigo, it does not account for tinnitus and deafness which also characterize the typical attack. With regard to the cochlea the evidence clearly indicated that streptomycin did not cause toxic destruction of sensory receptor units but, rather, had a salutary effect. It is difficult to imagine how destruction of sensory elements in the cristae, presumably taking place over a short period, could account for changes in auditory threshold occurring over a period of many years. The only explanation for these changes which comes to mind is variation in fluid pressure in the cochlea. This raises the question whether the major therapeutic effect of streptomycin is not concerned with restoration of normal fluid dynamics in the vestibular labyrinth and cochlea. Wersäll and Hawkins (13) offered the suggestion, based on pathological studies in the cat, that streptomycin is concentrated in the endolymph through the activities of the secretory cells in the crista. The toxic effects on secretory cells rather than on the hair cells of the crista might account for the major therapeutic action. This conclusion would be in line with the evidence (18-20) that idiopathic Ménière's disease is due to "hydrops" of the labyrinth.

The use of these patients as "naturally occurring human subjects" deserves brief comment. If it is assumed that OC and AN had "adequate" otolith function, then the absence of the nausea syndrome in the Slow Rotation Room suggests that suppression of canal function was responsible, a conclusion supported by findings on squirrel monkeys (9). The degree of suppression which was adequate to prevent symptoms, and, quite possibly more than adequate, was severe loss of canal function in one ear and partial loss in the other. Moreover, it keeps alive the possibility that drugs of the streptomycin series still hold promise in the treatment of motion sickness. At least loss of hearing is not a contraindication to their use if the present findings hold true for all subjects or patients tested.

If the same reasoning is applied in the case of ataxia, then these degrees of suppression of canal function are almost equivalent to total suppression insofar as maintenance of postural equilibrium is concerned. In short, a slight increase in caloric threshold levels, in terms of the total range (0° to 36° C), is responsible for almost total loss of this function. The rapid habituation to the bizarre stimulation of the semicircular canals as indicated by the oculogyral illusion is of theoretical and practical importance. If frequent head movements can be tolerated in the absence of the nausea syndrome, then the time required for habituation to a rotating environment may be greatly shortened.

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13. ABSTRACT Four patients who had received streptomycin sulfate in the treatment of Ménière's disease were evaluated in terms of the long-range effects of therapy and utilized as experimental subjects. The findings are reported in terms of a lack of return of their symptoms, and the effect of the drug on hearing, the semicircular canals, otolith organs, ataxia, and the Coriolis oculogyral illusion. An attempt was made to interpret the findings in terms of the etiology of idiopathic Ménière's disease, and the suggestion is made that it might represent a disturbance attributable to the secretory cells of the crista.			

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